PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT ISA/220) as well as, where applicable, item 5 below.
REG 710-A-PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/14142	23/05/2000	08/06/1999
Applicant		
REGENERON PHARMACEUTICALS, INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readble form.

   ☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   ☐ the text is approved as submitted by the applicant.

   ☒ the text has been established by this Authority to read as follows:

   MODIFIED CHIMERIC POLYPEPTIDES WITH IMPROVED PHARMACOKINETIC PROPERTIES

5. With regard to the **abstract,**

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

   ☐ as suggested by the applicant.

   ☐ because the applicant failed to suggest a figure.

   ☐ because this figure better characterizes the invention.

   ☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/14142

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 28-31, 33-40, 50, 51 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-8, 41-48 and partly 9-40, 49-51

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-8, 41-48 and partly 9-40, 49-51

An isolated nuleic acid molecule encoding a fusion polypeptide capable of binding a VEGF polypeptide comprising:

(a) a nucleotide sequence encoding a VEGF receptor component operatively linked to

(b) a nucleotide sequence encoding a multimerizing component,

wherein the VEGF receptor component is the only VEGF component of the fusion polypeptide and the nucleotide sequence (a) encodes essentially an Ig domain 2 of the extracellular domain of a first VEGF receptor and an Ig domain 3 of a second VEGF receptor.

Corresponding polypeptides, vectors, recombinant host cells, compositions, therapeutic applications. Where applicable, acetylated or pegylated polypeptides.

2. Claims: partly 9-21, 28-40,49-51

An isolated nucleic acid molecule comprising a nucleotide sequence encoding a modified Flt1 receptor fusion polypeptide, wherein the coding region of the nucleic acid molecule consists of the nucleotide sequence depicted either in Fig 13A-D (seq. ID 3) or in Fig. 14A-C (Seq. ID 5).

3. Claims: partly 9-21, 28-40,49-51

Idem as subject-matter 2, but limited to the sequence depicted in Fig.15A-C (Seq. ID 7).

4. Claims: partly 9-21, 28-40,49-51

Idem as subject-matter 2, but limited to the sequence depicted in Fig.16A-D (Seq. ID 9)

5. Claims: partly 9-40,49-51

A fusion polypeptide encoded by the nucleic acid sequence set forth in Fig. 10A-D (Seq. ID 1), which has been modified by acetylation or pegylation.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/14142

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C12N15/62 C12N5/10 C07K14/71 A61K38/17
A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DAVIS-SMYTH T ET AL: "THE SECOND IMMUNOGLOBULIN-LIKE DOMAIN OF THE VEGF TYROSINE KINASE RECEPTOR FLT-1 DETERMINES LIGAND BINDING AND MAY INITIATE A SIGNAL TRANSDUCTION CASCADE" EMBO JOURNAL,GB,OXFORD UNIVERSITY PRESS, SURREY, vol. 15, no. 18, 16 September 1996 (1996-09-16), pages 4919-4927, XP000611912 ISSN: 0261-4189	1-21, 28-51
A	the whole document ---	22-27
A	WO 97 44453 A (GENENTECH INC ;DAVIS SMYTH TERRI LYNN (US); CHEN HELEN HSIFEI (US)) 27 November 1997 (1997-11-27) cited in the application the whole document -----	1-51

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 August 2000	23. 11. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Galli, I

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Form PCT ISA 210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

[redacted]mation on patent family members

[redacted]ternational Application No
PCT/US 00/14142

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9744453 A	27-11-1997	US 6100071 A	08-08-2000
		AU 717112 B	16-03-2000
		AU 3060497 A	09-12-1997
		EP 0907733 A	14-04-1999
		JP 2000502357 T	29-02-2000
		NZ 332779 A	29-06-1999
		US 5952199 A	14-09-1999

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2 5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 14 December 2000 (14.12.00)	
International application No.: PCT/US00/14142	Applicant's or agent's file reference: REG 710-A-PC
International filing date: 23 May 2000 (23.05.00)	Priority date: 08 June 1999 (08.06.99)
Applicant: PAPADOPOULOS, Nicholas, J. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

24 October 2000 (24.10.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer: J. Zahra
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

3707913

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
N.79986 DMG/TJD		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/14142	23/05/2000	08/06/1999

International Patent Classification (IPC) or national classification and IPC
C12N15/12

Applicant
REGENERON PHARMACEUTICALS, INC. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/10/2000	30.08.2001

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Roscoe, R

Telephone No. +49 89 2399 2554

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/14142

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-90	as originally filed				

Claims, No.:

1-4,37-42	as originally filed				
5-36,43-52	as received on	20/08/2001	with letter of	13/08/2001	

Drawings, sheets:

1/55-55/55	as originally filed				

Sequence listing part of the description, pages:

1-34, filed with the letter of 05.10.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☒ furnished subsequently to this Authority in written form.
   - ☒ furnished subsequently to this Authority in computer readable form.
   - ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 10, 50 and 11-40, 51, 52 (all part).

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 10, 50 and 11-40, 51, 52 (all part).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-9, 41-49 and 11-40, 51, 52 (all part).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9, 11-49, 51, 52
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-9, 11-49, 51, 52
	No:	Claims	1-9, 11-49, 51, 52
Industrial applicability (IA)	Yes:	Claims	1-9, 11-27, 32, 41-49
	No:	Claims	28-31, 33-40, 51, 52

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

III. **No Opinion**

No opinion is expressed for unsearched subject-matter belonging to invention groups other than invention group I (see section IV)

IV. **Lack of Unity**

Present application comprises 5 different invention groups as defined in the International Search Report. Since applicant failed to pay additional search fees and consequently received an ISR relating to invention group I only, examination is similarly restricted to this invention group, i.e. claims 1-9, 41-49 and 11-40, 51, 52 (all part) insofar as these claims relate to a fusion polypeptide capable of binding VEGF substantially comprising (i) a multimerizing component and (ii) a VEGF receptor component consisting essentially of an Ig domain 2 from one receptor combined with Ig domain 3 of a second VEGF receptor.

V. **Reasoned statement on Novelty, Inventive Step and Industrial Applicability**

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

- **Novelty (Art.33(2) PCT)**

Neither D1 or D2 disclose a construct consisting essentially of (i) a multimerizing component and (ii) a VEGF receptor component consisting essentially of an Ig domain 2 from one receptor combined with Ig domain 3 of a second VEGF receptor.

No novelty objections.

- **Inventive Step (Art.33(3) PCT)**

Both D1 and D2 (scientific publication and corresponding patent application) show that VEGF receptor domains can be swapped. Binding specificity was further

shown to reside in the second Ig domain (Ig2). D1 also shows that Flt-1(Ig2+3) can bind to VEGF (see Fig.7A), yet the level of binding is reduced by about 10-fold. Fig.19 of the present application similarly shows a reduced binding of Flt-1(Ig2+3) compared to Flt-1(Ig1+2+3) - magnitude of difference is different but this depends on experimental conditions used. Looking at the aspect of ECM binding, Fig.23 of the present application demonstrates that constructs lacking Ig1 (and having different-source Ig2 and Ig3 domains) have substantially reduced ECM binding. This is the only significant technical effect that should be considered in the context of the assessment of inventive step. The prior art already shows a Ig2-Ig3 variant (D1 - discussed above). The prior art also suggests and demonstrates that domain swapping is possible. However, the Ig2-Ig3 variant of D1 was merely constructed to see which regions are necessary for binding. The loss of Ig1 resulted in a significant reduction in binding and would thus not be considered as desirable in the further development of VEGF receptor constructs. The skilled person did not know that deletion of Ig1 would substantially reduce ECM binding, i.e. he did not know the benefit of Ig1 removal. Hence, although the skilled person could have made constructs according to the present invention, it is not considered that he would have done so based on the knowledge available to him from the prior art.

The problem addressed by the applicant was the provision of an improved VEGF receptor. The Flt1Ig2/Flk1Ig3-comprising construct maintains high binding to VEGF. The same can not be said for the Flt1Ig2/Flt4Ig3-comprising construct. However, both constructs appear (according to example 29, to have improved pharmacokinetic properties without having completely lost binding ability). Hence, constructs that are proven to solve the problem addressed by the applicant are the Flt1Ig2/Flk1Ig3-comprising construct and the Flt1Ig2/Flt4Ig3-comprising construct (the construct of Fig.24 is considered acceptable too). These specific constructs can be considered inventive.

Generalization from these constructs in the manner performed by the applicant is not considered acceptable, since it encompasses matter that is not proven to, and can also not logically be expected to, solve a problem. It is thus not inventive. For example, constructs where the second Ig domain is derived from Flt4 would not be expected to work as a complete Flt-1 receptor with a Ig2 region from Flt4

does not bind VEGF according to D1 (p.4920, col.1). Further, there is no evidence that constructs where the natural relative positioning of the domains has been altered (i.e. Ig3 before Ig2) will have the desired properties.

Hence, the following claims contain non-inventive subject-matter: 1-9, 11-21, 23, 25, 26, 28-30, 32-49, 51, 52.

It is noted that modification of the lysine residues to reduce the basic charge is suggested in D2 (see p.18, l.1-3; p.19, l.20-21). The fact that applicant achieves this by acetylation is considered as a routine choice of a method of doing so. With regard to PEGylation, no useable prior art has been provided, yet it is noted that the invention relating primarily to PEGylated peptides was not searched.

- **Industrial Applicability (Art.33(4) PCT)**

For the assessment of the present claims 28-31, 33-40, 51, 52 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 28-31, 33-40, 51, 52 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

VIII. **Certain observations**

- **Clarity (Art.6 PCT)**

Claim 11 (and claims refering back thereto) - The DNAs from which peptide is produced are defined in an open-ended manner. Hence, in principle any fusion

peptide can be produced therefrom. This causes obvious novelty problems. No novelty objections have been raised on this basis for practical reasons, yet it is absolutely necessary to eventually clarify this issue.

Claim 12 should presumably refer to claim 11 and has been treated as though it is.

5. The isolated nucleic acid molecule of claim 1, wherein the nucleotide sequence encoding Ig domain 2 of the extracellular domain of the first VEGF receptor is upstream of the nucleotide sequence encoding Ig domain 3 of the extracellular domain of the second VEGF receptor.

6. The isolated nucleic acid molecule of claim 1, wherein the nucleotide sequence encoding Ig domain 2 of the extracellular domain of the first VEGF receptor is downstream of the nucleotide sequence encoding Ig domain 3 of the extracellular domain of the second VEGF receptor.

7. The isolated nucleic acid molecule of claim 1, wherein the multimerizing component comprises an immunoglobulin domain.

8. The isolated nucleic acid molecule of claim 1, wherein the immunoglobulin domain is selected from the group consisting of the Fc domain of IgG, the heavy chain of IgG, and the light chain of IgG.

9. An isolated nucleic acid molecule comprising a nucleotide sequence encoding a modified Flt1 receptor fusion polypeptide, wherein the coding region of the nucleic acid molecule consists of a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence set forth in Figure 13A-13D;

(b) the nucleotide sequence set forth in Figure 14A-14C;

(c) the nucleotide sequence set forth in Figure 15A-15C;

(d) the nucleotide sequence set forth in Figure 16A-16D;

(e) the nucleotide sequence set forth in Figure 21A-21C

(f) the nucleotide sequence set forth in Figure 22A-22C;

(g) the nucleotide sequence set forth in Figure 24A-24C; and

(h) a nucleotide sequence which, as a result of the degeneracy of the genetic code, differs from the nucleotide sequence of (a), (b), (c), (d), (e), (f), or (g) and which encodes a fusion polypeptide molecule having the biological activity of the modified Flt1 receptor fusion polypeptide.

10. A fusion polypeptide encoded by the isolated nucleic acid molecule of claim 1, 2, 3, 4 or 9.

11. A composition capable of binding a VEGF molecule to form a nonfunctional complex comprising a multimer of the fusion polypeptide of claim 10.

12. The composition of claim 11, wherein the multimer is a dimer.

13. The composition of claim 12 and a carrier.

14. A vector which comprises the nucleic acid molecule of claim 1, 2, 3, 4 or 9.

15. An expression vector comprising a nucleic acid molecule of claim 1, 2, 3, 4 or 9 wherein the nucleic acid molecule is operatively linked to an expression control sequence.

16. A host-vector system for the production of a fusion polypeptide which comprises the expression vector of claim 15, in a suitable host cell.

17. The host-vector system of claim 16, wherein the suitable host cell is a bacterial cell, yeast cell, insect cell, or mammalian cell.

18. The host-vector system of claim 16, wherein the suitable host cell is E. coli.

19. The host-vector system of claim 16, wherein the suitable host cell is a COS cell.

20. The host-vector system of claim 14, wherein the suitable host cell is a CHO cell.

21. A method of producing a fusion polypeptide which comprises growing cells of the host-vector system of claim 16, under conditions permitting production of the fusion polypeptide and recovering the fusion polypeptide so produced.

22. A fusion polypeptide encoded by the nucleic acid sequence set forth in Figure 10A-10D or Figure 24A-24C, which has been modified by acetylation or pegylation.

23. The fusion polypeptide of claim 22 wherein the modification is acetylation.

24. The fusion polypeptide of claim 22 wherein the modification is pegylation.

25. The fusion polypeptide of claim 23 wherein the acetylation is accomplished with at least about a 100 fold molar excess of acetylation reagent.

26. The fusion polypeptide of claim 23 wherein acetylation is accomplished with a molar excess of acetylation reagent ranging from at least about a 10 fold molar excess to about a 100 fold molar excess.

27. The fusion polypeptide of claim 24 wherein the pegylation is 10K or 20K PEG.

28. A method of decreasing or inhibiting plasma leakage in a mammal comprising administering to the mammal fusion polypeptide of claim 10.

29. The method of claim 28, wherein the mammal is a human.

30. The method of claim 29, wherein the fusion polypeptide is acetylated.

31. The method of claim 29, wherein the fusion polypeptide is pegylated.

32. The fusion polypeptide of claims 10 which specifically binds the VEGF receptor ligand VEGF.

33. A method of blocking blood vessel growth in a human comprising administering an effective amount of the fusion polypeptide of claim 10.

34. A method of inhibiting VEGF receptor ligand activity in a mammal comprising administering to the mammal an effective amount of the fusion polypeptide of claim 10.

35. The method of claim 34, wherein the mammal is a human.

36. The method of claim 34, used to attenuate or prevent tumor growth in a human.

43. The fusion polypeptide of claim 41 wherein the second VEGF receptor is Flk1.

44. The fusion polypeptide of claim 41 wherein the second VEGF receptor is Flt4.

45. The fusion polypeptide claim 41, wherein amino acid sequence of Ig domain 2 of the extracellular domain of the first VEGF receptor is upstream of the amino acid sequence of Ig domain 3 of the extracellular domain of the second VEGF receptor.

46. The fusion polypeptide of claim 41, wherein the amino acid sequence of Ig domain 2 of the extracellular domain of the first VEGF receptor is downstream of the amino acid sequence of Ig domain 3 of the extracellular domain of the second VEGF receptor.

47. The fusion polypeptide of claim 41, wherein the multimerizing component comprises an immunoglobulin domain.

48. The fusion polypeptide of claim 41, wherein the immunoglobulin domain is selected from the group consisting of the Fc domain of IgG, the heavy chain of IgG, and the light chain of IgG.

49. An fusion polypeptide comprising an amino acid sequence of a modified Flt1 receptor, wherein the amino acid sequence selected from

the group consisting of:

(a) the amino acid sequence set forth in Figure 13A-13D;

(b) the amino acid sequence set forth in Figure 14A-14C;

(c) the amino acid sequence set forth in Figure 15A-15C;

(d) the amino acid sequence set forth in Figure 16A-16D;

(e) the amino acid sequence set forth in Figure 21A-21C

(f) the amino acid sequence set forth in Figure 22A-22C; and

(g) the amino acid sequence set forth in Figure 24A-24C.

50. A method of decreasing or inhibiting plasma leakage in a mammal comprising administering to the mammal fusion polypeptide of claim 41, 42, 43, 44 or 49.

51. A method of inhibiting VEGF receptor ligand activity in a mammal comprising administering to the mammal an effective amount of the fusion polypeptide of claim 41, 42, 43, 44 or 49.